September 16, 1969

MEMORANDUM TO MR. AUSTERN

Re: Chemosol

The following memorandum records the discussion of the meeting of September 15, 1969, at Hazleton Laboratories. Present at this meeting were the following members of the subcommittee appointed by the industry research scientists: Dr. Nielsen (Reynolds), Dr. Burke (American) and Mr. Carpenter (Philip Morris); the following representatives of Hazleton: Mr. Gargus (technical), Dr. Sullivan (chemical), Mr. Jessup and Mr. Sebert (business); HTA and AJT.

At the beginning of the discussion Mr. Gargus distributed copies of the revised protocol, a copy of which is attached. Mr. Gargus stated that this protocol had been revised in accordance with the meeting of the research directors on September 10, 1969.

With regard to I, AJT stated that the research directors had decided that the objective should include a sentence stating that the relationship of skin painting to smoking and health had not been established. Mr. Gargus stated that he preferred to include such a statement in the final report of Hazleton and not in the objective section of the protocol.

With regard to II, Dr. Nielson explained that it had not been decided yet which company would manufacture the cigarettes to be utilized in this study. Each company has been assaying cigarettes of the University of Kentucky blend and the characteristics of this reference blend can be clearly documented. Dr. Hudson has never, to the knowledge of the subcommittee, employed cigarettes manufactured in accordance with the University of Kentucky blend.

HTA suggested that the industry subcommittee set forth in a separate document a detailed statement relating to the formulation of cigarettes for testing by Hazleton. Specifically, such statement should include each and every detail of manufacture.

Dr. Nielson stated that at the present time Lorillard has not been willing to manufacture the cigarettes. Reynolds might be willing to manufacture the cigarettes. To date it has only been decided that Lorillard will supply the tobacco. It will take approximately two weeks to manufacture the cigarettes.

HTA asked whether the 500,000 cigarettes contemplated by the present protocol would be sufficient. It was decided to increase the total number of cigarettes to be manufactured to one million, which would then be divided into two groups of 500,000 each. It would be up to Dr. Hudson to decide how the cigarettes should be sprayed. Neither Lorillard nor any other company was willing to provide spray guns or any other equipment for the spraying.

There was some general discussion of the operation of the smoking machines. In general, these machines smoke cigarettes and condensate is caught in a trap behind the cigarettes.

It was agreed by all present that prior to any testing by Hazleton, tpm, water and nicotine determinations should be run on the smoke of at least 200 of the untreated Kentucky blend cigarettes, and on at least 200 of the Chemosol treated Kentucky blend cigarettes. These tests should be conducted in accordance with the industry recommended methodology. HTA suggested that these initial determinations could be conducted at TITL. It was agreed by all those present that if either (a) the "tar" or nicotine yields varied between the untreated and treated cigarettes, or (b) varied within each of these groups, reconsideration would be made of the decision to proceed with biological testing by Hazleton.

HTA suggested the addition of organoleptic tests as well as the tests described in the protocol. It was decided that such tests would be considered after completion of the tests described in the protocol.

HTA further suggested that the companies should specify in writing the type of cigarette paper to be employed in these tests. It was decided that this information would be included in the separate protocol to be prepared by the subcommittee, which would include details of the manufacture of the cigarettes.

On III.A paragraph 2, HTA suggested that the first sentence be changed to read that "appropriate laboratory equipment, designated by the sponsor, will be utilized to smoke the samples in rotation." Also on III.A it was agreed that while "tar" and nicotine tests would be conducted on the smoke prior to tests by Hazleton, specifications of these tests would be confined to the second protocol to be prepared by the subcommittee and would not be included in the protocol prepared by Hazleton.

Mr. Sebert stated that Hazleton would need a time schedule for the beginning of work in order to schedule its operations. HTA explained the difficulties of adhering to precise time schedules, in view of the fact that nine companies were participating in this project. Mr. Sebert stated that if for any reason the work should abort, the industry would merely pay the cost of time and materials for work done to the date of abortion. In this regard, it should be noted that the budgeted costs for chemical work are twice as much as the budgeted costs for biological work. In order to avoid excessive costs in the event that the cigarettes vary in "tar" and nicotine content, it was decided that prior to the completion of "tar" and nicotine testing by the sponsors, Hazleton would prepare the machines for operation but would not gather condensate for the tests.

The industry agreed to supply smoking machines to Hazleton to gather condensate and technical details for their operation. As an alternative to supplying these machines, the industry can suggest to Hazleton machines that could be purchased and then reimburse Hazleton for their purchase.

Also on III.A, there was a lengthy discussion relating to paragraph four and quality control tests to be conducted by Hazleton. Sentences two and three of paragraph four as written were eliminated and replaced with a sentence providing that "Hazleton shall conduct, for quality control purposes, such routine chemical tests as are necessary to ensure continuity and quality control."

Gargus stated that as part of its routine quality control tests, Hazleton would determine the benzo(a)pyrene content of condensate from both treated and untreated cigarettes. The results of these routine periodic benzo(a)pyrene determinations would be included in the laboratory notebooks of Hazleton. HTA suggested that Hazleton consider dropping such a routine benzo(a)-pyrene test from this project in view of the claims made by Chemosol for benzo(a)pyrene reduction, and in view of the decision of the research directors at the meeting of September 10, 1969, that no decision would now be made as to the test for benzo(a)pyrene content, and that such a decision would be made at the termination of the biological tests.

Other routine chemical quality control tests are likely to include nicotine, polycyclic hydrocarbons, water content, and perhaps nitrate content. HTA explained that it may be necessary to specify the tests being conducted by Hazleton in the event that Chemosol becomes concerned that by detailed chemical analyzes its formula may be discovered, contrary to the understanding by which it was agreed that the sponsors would not make an effort to determine the Chemosol formula.

With regard to III.B, HTA asked Mr. Gargus to clarify the purpose of groups No.1, No.2 and No.3, set forth on page 3 of the protocol. Mr. Gargus explained that these three groups were controls; that group No.1 is designed to show what happened to mice who had no treatment at all; group No.2 was intended to show what happened to mice who were treated with only acetone, i.e., the solvent used in painting in both treated and untreated condensate on mice. It was anticipated that groups No.1 and No.2 would show very few tumors. Group No.3 was intended as a positive control, i.e., it was intended to show that by treating this type of mouse with a known carcinogenic agent tumors would be obtained. The choice of benzo(a)pyrene in group No.3 was not required. Any known carcinogenic agent, regardless of whether it was found in cigarette smoke, would serve the intended purpose. Mr. Gargus explained that benzo(a)pyrene had been employed because it was the best known carcinogenic agent and the one generally used in experiments of this type. (Mr. Gargus later stated that Hazleton was presently employing benzo(a)pyrene as the positive control in other work being done by Hazleton for the HEW.) HTA suggested that Hazleton employ some control other than benzo(a)-pyrene in view of the repeated assertions made by Chemosol for benzo(a)pyrene reduction, and in view of the psychological implications of "benzo(a)pyrene" in the cigarette controversy. Mr. Gargus rejected these suggestions, and Mr. Jessup stated that unless Mr. Gargus was satisfied on the scientific grounds, Hazleton would not enter into the contract. As written, page 3 of the protocol has a misprint in describing group No.3. The number 20 should be 20 γ (20 micrograms, or 20/1000 mg.).

Mr. Gargus stated that the population of mice employed was sufficiently large to draw statistical conclusions. The mice cost approximately 50 cents each.

It was agreed that there would be no progress reports furnished by Hazleton to the industry during the course of the work. The industry would be informed that work was proceeding by bills sent to the sponsors. In addition, the members of the industry subcommittee might from time to time visit Hazleton to make certain that work was proceeding. It was also contemplated that technical discussions would be required between Hazleton and industry representatives throughout the tests as provided for in the protocol, by which the industry is required to furnish technical assistance. It was decided that the matter of interim progress reports would be totally omitted from the protocol.

With regard to the duration of the work, the first full sentence on page 4 should be revised to state that "the duration of the dermal part of this study is contemplated to be two years."

Mr. Sebert stated that Hazleton would not issue information to Chemosol representatives or to any other third party.

With regard to publication of the results, Mr. Gargus suggested that Hazleton be authorized to publish the results of its study in a scientific journal even prior to submission of a report by Hazleton to the sponsors, and prior to Hazleton's submission of its final results to the sponsors. In this way, Mr. Gargus stated, Hazelton could secure its scientific reputation by making sure that Hazelton published its test results. Under this approach no-one would see the Hazelton results until they were published. HTA disagreed with this suggestion, stating that the sponsors were paying for the work and should certainly see the results before they were published. In addition, publication is generally a matter of the sponsors' discretion.

Mr. Jessup suggested that at the end of the study and before the final report was written there should be a discussion between Mr. Gargus and the industry subcommittee, at which time the results would be discussed and Hazleton could inform the industry representatives of the type of paper which was contemplated. It was agreed that a provision would be included in the contract relating to publication.

HTA stated that individual companies may want to criticize the Hazleton work, and it should be understood that each company should have the right to do so.

Mr. Gargus suggested that part of the objective of the study should be publication and that if this were the case no final report would be required until after publication. Hazleton would be willing to provide a copy of the manuscript to the nine sponsoring companies to review before publication. Mr. Gargus stated that recognition of the sponsors would be included in the paper. Mr. Jessup recognized that Hazleton needed permission from the sponsors to publish.

HTA agreed to clarify with Chemosol representatives the fact that Dr. Hudson would not be permitted to spend time at Hazleton after the cigarettes were delivered to Hazleton. HTA suggested that Dr. Hudson might be permitted one visit. Dr. Burke stated that Dr. Hudson should, if possible, be kept away from Hazleton but, if necessary, Dr. Hudson should only be permitted to come to Hazleton in the presence of industry scientists and industry counsel.

Mr. Gargus stated that if Hazleton could not get a provision in the contract relating to publication Hazleton would not proceed with the work. HTA stated that he could not respond to this point in the absence of instructions from his principals. HTA further suggested that AJT should be present at any future technical discussions between Hazleton and industry representatives.

It was agreed that the industry subcommittee, working with Mr. Gargus, would revise the protocol in accordance with this discussion and forward it to the research directors. The subcommittee would promptly prepare the second protocol providing the detailed description of the preparation of the cigarettes.

HTA met with Mr. Sebert to discuss costs and a contract. Mr. Sebert stated that Hazleton's costs submitted to the research directors on September 10, 1969 ($100,500 . . . + $50,000) were merely estimates, and not maximum or minimum costs. In the event that the cost of labor and materials is less than the estimated amount, the sponsors will only pay the actual amount for labor and materials. In the event that the costs exceed

this estimate, the companies will pay the additional amount. Mr. Sebert did state that in the event that it becomes apparent that actual costs will exceed the estimate then Hazleton will so inform the sponsors.

* * *

The following two items were not discussed at the meeting:

(1) In view of the original August 1, 1967, proposal to replicate Dr. Hudson's work, what is the justification for:

(a) confining the biological tests to skin painting and ignoring subcutaneous injection, and

(b) employing a methodology for skin painting tests different to that employed by Dr. Hudson.

(2) There was no discussion of coding. For example, whether each cigarette in each of the two batches is to be marked, and if so whether they will be marked with an "X" or a "Y" or color coded, and what will be the mechanics of this coding.

Allan J. Topol

AJT:emf
Enclosure